REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-12, 14, 15, 17-28, 41 and 42 are pending in the instant application. Claims 29-40, which are directed to non-elected subject matter, and Claims 24 and 25 are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional application(s) to non-elected subject matter. The limitations of Claims 13 and 16, which also are cancelled herein without prejudice or disclaimer, are incorporated into amended Claim 1. Claims 41 and 42, which find basis in original Claims 1 and 28, respectively, are added herein. Claim 43 also is added herein. Basis for added Claim 43 may be found in original Claims 24 and 25 and in the specification, for example, at page 40, lines 26-28 and at page 42, lines 8-21.

Claim 1 is amended herein to clarify the subject matter of the claim and its dependents. As amended, Claim 1 clarifies that the method is a multiplexed method of detecting a plurality of target polypeptides in a sample, such as, for example, all proteins involved in a particular disease. The amendment further clarifies that the target polypeptides are complexed with specific polypeptide-binding components that are displayed on genetic packages. Each genetic package has a predetermined marker component that is indicative of a polypeptide-binding component that is displayed on the genetic package. Once a complex of a target polypeptide with a polypeptide-binding component on a genetic package is identified, the predetermined marker component indicative of that polypeptide-binding component is used to detect the target polypeptide in genetic packages that have formed complexes. Basis for the amendment may be found in original claims 1, 13 and 16 and in the specification, for example, at page 3, lines 23-26; page 4, lines 17-19; page 5, lines 2-6; page 5, line 21 to page 6, line 3; page 23, lines 24-29; page 24, lines 25-29; Figure 1 and its description at pages 27 and 28; page 28, lines 2-6; page 29, lines 12-13; page 40, lines 1-9; and page 44, lines 15-24.

Claim 12 is amended herein to clarify the description of the phage that is an element of the claim, by replacing the symbol "λ" with the word lambda. Claims 14, 15 and 17 are amended herein to change their dependency from Claims 13 and 16 to Claim 1, which as

amended herein incorporates the limitations of Claims 13 and 16. Claim 17 also is amended herein to clarify that the related marker components are mutants or variants derived from the same gene. Basis for this amendment may be found in the specification, for example, at page 41, lines 3-20; page 42, lines 8-11; and page 43, lines 21-24. No new matter is added.

REJECTION OF CLAIMS 1-28 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-28 are rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter. It is alleged that, while the specification is enabling for an assay in which polypeptide-binding components displayed on a genetic package containing a predetermined marker are attached to a solid substrate and then contacted with the sample, there is no reasonable enablement for a method where only the genetic package is contacted with a sample.

The Examiner further appears to allege, in paragraph 4 on page 2 of the Office Action, that the specification is not enabling for the method as claimed because attachment of the polypeptide-binding component to a solid substrate is "critical" to the practice of the invention, as is a wash step to remove unbound genetic packages and avoid detection of "false positives." It is respectfully submitted that the assertion that "critical" steps are missing goes to indefiniteness and not scope of enablement. Therefore, although this portion of the rejection is addressed where applicable herein, it is more fully addressed in response to the rejection on indefiniteness grounds, discussed below.

Reconsideration of the grounds for rejection is respectfully requested in view of the amendments herein and the following remarks. It is respectfully submitted that this rejection is rendered moot with respect to claims 13, 16, 24 and 25, which are cancelled herein. Furthermore, It is respectfully submitted that claims 3-5, which recite that the target polypeptides are immobilized, are outside the purview of this rejection.

Relevant law

To satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112,

first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed*. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Application of In re Wands factors to the methods as instantly claimed

Scope of the claims

Claim 1 is directed to a multiplexed method of detecting a plurality of target polypeptides in a sample by (a) contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component; (b) identifying complexes of the plurality of target

polypeptides with the displayed polypeptide-binding components on the genetic packages; (c) optionally amplifying either the genetic packages that have formed complexes or the marker components that are in the genetic packages that have formed complexes; and (d) detecting marker components in the genetic packages that have formed complexes, thereby detecting the plurality of target polypeptides. Dependent claims 2-5 specify the types of target polypeptides, binding of the target polypeptides or the genetic package to a solid support, the type of solid support, and a washing step after complex formation on a solid support. Dependent claims 6-9 specify numbers of the plurality of target polypeptides that are detected by the method of claim 1. Dependent claim 10 specifies the types of samples, and dependent claims 11 and 12 further specify the nature of the genetic package. Claims 14 and 15 depend on Claim 1 and specify the numbers of polypeptide-binding components in the method. Claim 17 is directed to the method of claim 1 where the marker components are variants or mutants derived from the same gene. Claim 18 specifies the type of polypeptide-binding component of claim 1, Claim 19 is directed to the method of claim 18 and specifies that the polypeptide-binding component that is an antibody or antibody fragment as set forth in claim 18 contains one or more antigen recognition regions, and claim 20 specifies techniques by which the marker of claim 1 is detected. Claim 21 specifies that the technique of mass spectrometry is used to detect the markers. Claim 22 is directed to the method of claim 1, that includes a further step of determining an amount of the marker component. Claim 23 specifies a further step in the method of claim 22 of correlating the amount of the marker component to an amount of at least one or more polypeptides in the sample. Claim 26 is directed to the method of claim 1 where the genetic package contains a surface and where the marker component contains a nucleic acid encoding a polypeptide that is expressed on the surface of the genetic package. Claim 27 is directed to the method of claim 1 where the predetermined marker component contains a nucleic acid fragment. Claim 28, which specifies the types of amplification reactions used to amplify marker component, depends on the method of claim 27.

Added claims 41 and 42 specify amplification of the genetic packages prior to detection of the markers, including the types of amplification reactions (claim 42). Added claim 43 depends on claim 17 and specifies that the gene is hemoglobin.

As discussed below, the specification adequately teaches each of steps (a) through (d) of the method of claim 1, including specific features of each of the steps as set forth in the various dependent claims.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the specification: guidance and examples

The specification teaches in great detail each of the steps of the methods as claimed. The specification (*see*, *e.g.*, page 23, line 23 to page 24, line 22) describes how the instant methods are multiplexed assays in which tens to hundreds of detection events can simultaneously be performed to monitor complex systems, such as mixtures of tens of hundreds of target proteins of interest, by simultaneously detecting their expression level and/or functional states. The specification teaches (*see*, *e.g.*, page 4, line 12 to page 5, line 13; page 44, lines 15-24) that the method is performed by contacting a sample, such as blood or other body fluid or tissue containing target polypeptides of interest, with genetic packages, such as phage, viruses or bacteria, that display a plurality of polypeptide-binding components. The specification teaches that each polypeptide-binding component can be associated with a different predetermined marker component that is in the genetic package. Thus, the plurality of target polypeptides complexed with a plurality of polypeptide-binding components can be simultaneously detected by simultaneous detection of the different predetermined marker components in the genetic packages that have formed complexes.

The specification teaches that at the time of filing, several technologies were available for protein expression analysis and for analysis of complex mixtures of proteins, including protein-protein interactions (*see*, *e.g.*, page 2, line 15 to page 3, line 15), such as various immunodetection methods, direct visualization, two-dimensional gel systems and the use of protein-reporter gene conjugates. The specification further teaches that in some embodiments of the claimed methods, either the genetic package or the target polypeptides are bound to a solid support (*see*, *e.g.*, page 5, lines 14-16). As incorporated by reference in the specification and made of

record in the instant application, there clearly existed heterogeneous (*e.g.*, using a solid support) and homogeneous (single, *e.g.*, solution phase) methods of studying protein-protein interactions at the time the instant application was filed.

The specification further describes in great detail each of the components and steps of the method, providing numerous examples. The specification at page 25, line 28 to page 27, line 6, describes in great detail the samples containing the target polypeptides, such as various body fluids, tissues, organs and cells. The specification teaches that the samples can contain anywhere from 3 to about 10,000 target polypeptides. The target polypeptides bind to polypeptide-binding components that are displayed on genetic packages, and a predetermined marker component in the genetic package, indicative of its displayed polypeptide-binding component, is used as a signal to detect bound target polypeptides. The specification teaches that in some embodiments, the target polypeptides are bound to a solid support and any unbound polypeptide-binding components are removed by washing.

The specification goes on to describe types of polypeptide-binding components, such as an antibody or portion thereof displayed on a bacteriophage (page 27, lines 7-24). The specification provides in great detail (page 27, line 25 to page 29, line 10; Figure 1) how to conduct an exemplary assay for multiplexed binding, amplification of the bound phage or its predetermined marker component, and detection of target polypeptides by detecting the predetermined marker components that each signal a different polypeptide-binding domain to which a target polypeptide is bound.

The specification describes and incorporates by reference numerous examples of genetic packages and of polypeptide-binding components (page 29, line 11 to page 31, line 16), including their preparation and purification. Further, for example, page 31, line 17 to page 39, line 15 of the specification describes in extensive detail how to prepare highly diverse, even randomized, libraries of genetic packages, including purification of the components for their assembly.

The specification for example at page 39, line 16 to page 44, line 12, extensively describes predetermined marker components, such as polypeptides or polynucleotides, and how each marker component signals a unique polypeptide-binding component that binds to a target polypeptide. The cited section also describes

how to prepare variants or mutants of a predetermined marker, such as hemoglobin, such that the resulting plurality of predetermined markers are distinct yet simultaneously resolvable and detectable to facilitate high-throughput, multiplexed detection.

The specification, for example, at page 44, line 13 to page 62, line 7, describes, incorporates by reference, and exemplifies practice of the claimed methods. These teachings include: how to contact a sample with a genetic package; how to enrich for and concentrate bound target polypeptide; the use of solid substrates in some embodiments and their various types; how to test for the effectiveness of binding; exemplary amplification techniques such as PCR, ligase chain reaction, Qβ-replicase amplification and components, including expression vectors and enzymes; how to optimize amplification of the genetic package or predetermined marker component; detection techniques, including mass spectrometry, NMR, hybridization, immunodetection, fluorescent detection, chemiluminescent detection, colorimetric detection, electrophoretic detection, detection of arrays, surface plasmon resonance, electrochemiluminescent detection and electrochemical detection.

Knowledge of those of skill in the art

As made of record by Applicant and as incorporated by reference in the application, it is clear that a broad body of knowledge existed in the art related to methods and reagents for analyzing protein-protein complexes and interactions at the time of filing. The sections of the specification cited above in discussing the "Teachings of the Specification" describe and incorporate by reference numerous articles directed to various steps of the instant method, including: protein-protein binding assays; identifying protein-protein complexes, including proteins that are complexed to polypeptides that are displayed on genetic packages such as phage, bacteria or viruses; amplification of the complexed genetic packages or predetermined marker components in the genetic packages; preparing variants of the marker components by, *e.g.*, random mutagenesis to produce a plurality of marker components; techniques for detecting a plurality of markers such as polypeptides or polynucleotides; and methods of correlating detection of the plurality of markers with the detection and/or quantitation of a plurality of target polypeptides in a sample.

The Examiner alleges that the specification is enabling only for a method in which the polypeptide-binding components are attached to a solid substrate, and a method that includes

a wash step. First, Applicant respectfully submits that as discussed in detail above, the specification teaches that in embodiments where a solid support is used, *either* the polypeptide-binding component *or* the sample containing target polypeptides can bound to a solid support, not just the polypeptide-binding component.

Further, Applicant respectfully submits that as the specification teaches and incorporates by reference, at the time of filing, several technologies were available for protein expression analysis and for the analysis of complex mixtures of proteins and protein-protein interactions– these methods include various immunodetection methods, direct visualization, two-dimensional gel systems and the use of protein-reporter gene conjugates (*see, e.g.*, page 2, line 15 to page 3, line 15). These methods do not necessarily require a solid substrate. Therefore, it is not essential for either the genetic package or the sample to be bound to a solid support – the complexes between the genetic packages and the target polypeptides in the sample can be formed in solution or any other single (homogeneous) phase and analyzed according to a variety of routine techniques that were known at the time the instant application was filed.

While a solid substrate may be used in some embodiments of the claimed method, such as a sandwich assay that is an alternative to an ELISA (enzyme-linked immunosorbent assay), numerous immunodetection, direct visualization, chromatographic and gel separation methods were available at the time of filing for the analysis of protein-protein interactions and complexes in solution phase. At the time the instant application was filed, numerous methods for separating and/or analyzing protein-protein complexes in solution phase were known, including complexes where one of the protein components is on a genetic package such as a phage. For example, at the time the instant application was filed, phage-antigen complexes had been precipitated from a solution of complex protein mixtures by polyethylene glycol (PEG) precipitation, without non-specific protein contamination (Telleman *et al.*, Biotechniques, 29(6):1240-1248 (2000); attached hereto). Similarly, Demartis *et al.* (J. Mol. Biol., 286(2):617-633 (1999); attached hereto) describes the isolation of phage-peptide complexes from solution by capture with magnetic beads or by PEG precipitation; the complex can then be dissociated if desired by the addition of calcium chelators. Several techniques including PEG precipitation, Sephacryl S-200 chromatography, DEAE-cellulose chromatography, Sepharose CL-2B chromatography, Q-Sepahrose chromatography, Fast Protein Liquid Chromatography (FPLC), gel filtration, affinity

chromatography and velocity gradient centrifugation have been used to isolate and analyze protein complexes that are formed in solution (Wang *et al.*, Mol. Cell. Biol., 21(14):4604-4613 (July 2001); Sinclair *et al.*, Biochem. Mol. Biol. Int., 31(5):911-922 (1993); Sarisky *et al.*, Biochem. Biophys. Res. Commun., 177(2):757-763, (1991); Li *et al.*, J. Cell. Biochem., 53(4):405-419, (1993); attached hereto). Purification of protein-protein complexes in solution by electrophoresis on native gels was known at the time the instant application was filed (Werhahn et al., Plant Physiol., 125(2):943-954 (2001); Fountoulakis *et al.*, Anal. Biochem., 208(2):270-276 (1993); attached hereto). Additionally, homogeneous enzyme-based immunoassays were available in the art at the time of filing (Morris *et al.*, Ther. Drug Monit., 14(3):226-233 (1992); attached hereto).

Further, as demonstrated above, at the time the instant application was filed, numerous methods for identifying and analyzing protein-protein complexes were known to those of skill in the art, and not all of the above methods require a wash step to remove unbound protein or genetic package. Moreover, claim 1 as amended herein specifies that the marker components are detected in genetic packages that have formed complexes; therefore, one of skill in the art would know that any unbound genetic packages must be washed away or otherwise removed prior to detection of the marker components. It is therefore respectfully submitted that a step of washing unbound genetic packages is not "critical" to the claimed method because it is not always needed and when needed it is a routine step that one of skill in the art would know to perform when following the recited steps of the method.

Predictability

As discussed above, the level of knowledge and skill in the art in the analysis of protein-protein complexes, including complexes with genetic packages, was high as of the effective filing date of the instant application. Many techniques for studying protein-protein complexes on a solid support or in solution, with or without a wash step, were known, and the specification also teaches that a variety of techniques were available, only some embodiments of which include the use of a solid support. Therefore, the teachings of the specification, when combined with the knowledge of those of skill in the art, including the knowledge of routine procedures in the art, provides the ability to predictably apply any homogeneous or heterogeneous protein complexation and identification procedure, whether or not the protein components are bound to a solid support, and whether or not a step of washing is required, to the instant multiplexed methods of detecting a plurality of target polypeptides in a sample.

Conclusion

In light of the extensive teachings and examples in the specification for each of the steps of the claimed methods, the knowledge of those of skill in the art, the fact that it is predictable given the teachings of the instant application and the state of the art at the time of filing to form and identify protein-protein complexes, including complexes with genetic packages, in solution or on a solid support and with or without a wash step, Applicant respectfully submits that it would not require undue experimentation for one of skill in the art to make and use methods as taught by the instant application for multiplexed detection of a plurality of target polypeptides in a sample by complexation with polypeptide-binding components on genetic packages and detection of predetermined marker components indicative of the polypeptide-binding components. Accordingly, a consideration of the factors enumerated in In re Wands leads to the conclusion that undue experimentation would not be required to perform the steps of the method as claimed, regardless of whether a solid support or a wash step is used.

Policy Considerations

As discussed above, the instant methods are directed to a multiplexed method of detecting a plurality of target polypeptides in a sample by (a) contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component; (b) identifying complexes of the plurality of target polypeptides with the displayed polypeptide-binding components on the genetic packages; (c) optionally amplifying either the genetic packages that have formed complexes or the marker components that are in the genetic packages that have formed complexes; and (d) detecting marker components in the genetic packages that have formed complexes, thereby detecting the plurality of target polypeptides. The Office Action acknowledges that the steps of the method of detection as claimed are enabled when the polypeptide-binding component is attached to a solid support and when there is a wash step to remove uncomplexed material. As discussed above, however, the specification describes and those of skill in the art knew that there were numerous methods of preparing and identifying protein-protein complexes, including methods that do not employ a solid support or a wash step, at the time the instant application was filed. Accordingly, Applicant is entitled to claims

that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant provides the public with exemplary methods of forming complexes between genetic packages and target polypeptides on solid supports and separating unbound genetic packages, and Applicant further describes that many methods of analyzing protein-protein complexes and interactions were known at the time the application was filed. As a broad body of knowledge was available in the area of protein-protein interactions and identification in solution or solid phase at the time the application was filed, it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to methods in which the genetic package or target polypeptide is bound to a solid support and unbound material is removed with a wash step. To limit an Applicant to claims involving the specific materials disclosed in examples so that a competitor, seeking to avoid infringement can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts"). *See, e.g.*, In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require Applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. If Applicant is required to limit the claims to forming complexes between genetic packages and target polypeptides on solid supports and washing unbound protein, then those of skill in the art could by virtue of the teachings of this application readily practice what is claimed by forming complexes between genetic packages and target polypeptides in solution with no solid support and identifying them by a variety of methods, including those that do not require a wash step, such as PEG precipitation or homogeneous immunoassays. To permit that is simply not fair. The instant application exemplifies binding of a plurality of target polypeptides to the polypeptide-binding components of genetic packages on solid supports, and analyzing the resulting complexes after washing away unbound protein. Having done so, it is now routine for others to carry out the steps of the instant methods on complexes between genetic packages and target polypeptides that are formed in solution or in a

homogeneous, single phase. Those of skill in the art should not be permitted to make such minor modifications by substitution of the technique of forming and identifying the complexes.

REJECTION OF CLAIMS 1-28 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-28 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Various reasons for this rejection are provided, each of which is addressed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant Law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an Applicant is entitled to be its own lexicographer (see, e.g., MPEP 2111.01). The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); *See, also, Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed.Cir. 1997). The words of a claim must be given their plain meaning unless applicant has provided a clear definition in the specification. *In re Zletz*, 893, F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed.Cir. 1989). The claims are definite if they "make clear what subject matter they encompass and thus what the patent precludes others from doing." *In re Spiller*, 182 USPQ 614 (CCPA 1974).

Analysis

1) Claim 1 is rejected as being indefinite because it allegedly is unclear what relationship exists between the polypeptide-binding component and the marker component. It is further alleged that that it is unclear how the target polypeptides are detected using the aforementioned two components because the two components are unrelated to one another and therefore the marker component can be detected regardless of whether the polypeptide-binding component binds one or more target polypeptides. Claim 1 as amended herein recites that each genetic package has a predetermined marker component that is indicative of its displayed polypeptide. Thus, the relationship between the polypeptide-binding component and the marker component is clear. Claim 1 also is amended herein to clarify that the marker component is detected in genetic packages that have formed complexes. Thus, as amended, the marker component is not detected unless it is present in a genetic package that has formed a complex with a target polypeptide. Basis for the amendment may be found in original claims 1, 13 and 16 and in the specification, for example, at page 3, lines 23-26; page 4, lines 17-19; page 5, lines 2-6; page 5, line 21 to page 6, line 3; page 23, lines 24-29; page 24, lines 25-29; Figure 1 and its description at pages 27 and 28; page 28, lines 2-6; page 29, lines 12-13; page 40, lines 1-9; and page 44, lines 15-24. No new matter is added.

In light of the above, it is respectfully submitted that Claim 1 and claims 2-28 dependent thereon are definite.

2) Claim 1 also is rejected as being indefinite because the claim allegedly omits essential steps, such as a step of attaching a polypeptide binding component to a solid substrate, a wash step to remove unbound material, and a release step for releasing the polypeptide before the amplifying step. This rejection is respectfully traversed.

As discussed under the "Relevant Law" above, the amount of detail required to be included in the claims is not to be viewed in the abstract, but in conjunction with whether the

specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); *See, also, Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. It is unnecessary and unduly limiting to recite steps routine to those of skill in the art at the time the application was filed, such as wash steps and release of a bound polypeptide prior to analysis. Claim 1 as amended specifies that complexes of genetic packages with the target polypeptides are identified and the marker component is detected in genetic packages that have formed complexes. It is clear from the language of the claim to one of skill in the art that the complexes must be identifiable and, if necessary, separable from the uncomplexed material before detection of the marker component. As discussed in great detail when addressing the rejection on grounds of inadequate scope of enablement, the steps of identifying protein-protein complexes in a mixture containing unbound proteins and other material were well-known to those of skill in the art at the time the instant application was filed.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The instant claims are definite because the steps of (a) contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component; (b) identifying complexes of the plurality of target polypeptides with the displayed polypeptide-binding components on the genetic packages; (c) optionally amplifying either the genetic packages that have formed complexes or the marker components that are in the genetic packages that have formed complexes; and (d) detecting marker components in the genetic packages that have formed complexes, thereby detecting

the plurality of target polypeptides, adequately define the metes and bounds of the claimed subject matter in light of the disclosure in the specification and what is known to those of skill in the art.

As discussed above in the traverse of the enablement rejection, the specification teaches that at the time of filing, several technologies were available for protein expression analysis and for analysis of complex mixtures of proteins, including protein-protein interactions (*see*, *e.g.*, page 2, line 15 to page 3, line 15), such as various immunodetection methods, direct visualization, two-dimensional gel systems and the use of protein-reporter gene conjugates. As incorporated by reference in the specification and made of record in the instant application, there clearly existed heterogeneous (*e.g.*, using a solid support) and homogeneous (single, *e.g.*, solution phase) methods of studying protein-protein interactions at the time the instant application was filed.

Furthermore, as discussed above in addressing the rejection for alleged inadequate scope of enablement, numerous methods for identifying and/or purifying protein-protein complexes in solution phase, including methods that do not require a wash step, were known. For example, phage-antigen complexes had been precipitated from a solution of complex protein mixtures by polyethylene glycol (PEG) precipitation, without non-specific protein contamination and without requiring a wash step (Telleman *et al.*, Biotechniques, 29(6):1240-1248 (2000); attached hereto). Similarly, Demartis *et al.* (J. Mol. Biol., 286(2):617-633 (1999); attached hereto) describes the isolation of phage-peptide complexes from solution by capture with magnetic beads or by PEG precipitation. As discussed above, other techniques including PEG precipitation, Sephacryl S-200 chromatography, DEAE-cellulose chromatography, Sepharose CL-2B chromatography, Q-Sepahrose chromatography, Fast Protein Liquid Chromatography (FPLC), gel filtration, affinity chromatography, velocity gradient centrifugation and native gel electrophoresis have been used to isolate and analyze protein complexes that are formed in solution. Additionally, homogeneous enzyme-based immunoassays were available in the art (in addition to ELISA assays) at the time of filing (Morris *et al.*, Ther. Drug Monit., 14(3):226-233 (1992); attached hereto).

Therefore, it is respectfully submitted that one of skill in the art, given the methods as instantly claimed, would recognize (i) the scope/boundaries of the claimed subject matter; and (ii) the various techniques (heterogeneous and homogeneous

phase) by which protein-protein complexes can be identified and analyzed in a sample. No further elaboration is necessary to render definite each of the steps of the claimed method. It is respectfully submitted that in this instance, the claims reasonably apprise the skilled artisan of the scope and utilization of the claimed methods. Therefore, it is respectfully submitted that Claim 1 and claims 2-28 dependent thereon are not indefinite.

3) Claim 12 is rejected as being vague and indefinite because of the use of a symbol "λ." This rejection is obviated by replacing the symbol with the word "lambda." It is respectfully submitted that "lambda phage" is an art-recognized term used to identify a type of phage that is well-characterized and well-known to those of skill in the art.

4) Claim 13 is rejected as being indefinite because it allegedly is unclear whether a "plurality of bio-displayed polypeptide-binding components" refers to many of the same kind of bio-displayed peptide or many different kinds of bio-displayed peptides. It is further alleged that Claim 13 is indefinite because it is unclear what relationship exists between the genetic package and the bio-displayed polypeptide-binding components. This rejection is rendered moot by cancellation of Claim 13 herein.

Further, as discussed above, Claim 1 as amended herein incorporates the limitations of Claim 13 and clarifies the subject matter. For example, Claim 1 as amended herein clarifies that the method is a multiplexed method of detecting a plurality of target polypeptides in a sample. As the specification describes (*see*, *e.g.*, page 25, lines 6-16), the claimed assays are useful for analyzing several target polypeptides in a single assay such as, for example, all proteins involved in a particular disease. In addition, the plain meaning of the term "multiplexed" is "involving or including several <u>different</u> things, parts of or factors" (Encarta Dictionary: English; emphasis added). It therefore is clear, from the plain meaning of the phrase and in light of the specification, that a multiplexed assay for detecting a plurality of target polypeptides in a sample refers to different types of target polypeptides that are present in a sample and not multiple copies of the same target polypeptide molecule. The amendment further clarifies that the target polypeptides are complexed with specific polypeptide-binding components that are displayed on genetic packages, and that each genetic package has a predetermined marker component that is indicative of a polypeptide-

binding component that is displayed on the genetic package. Therefore, it is clear that different polypeptide-binding components bind to the plurality of target polypeptides and are detected by signal marker components, each of which is indicative of a particular displayed polypeptide-binding component. Further, the relationship between the polypeptide-binding component (also referred to as a bio-displayed polypeptide-binding component in the specification) and the marker component is clarified as one (the marker component) being indicative of the other (the polypeptide-binding component).

5) Claim 16 is rejected as being indefinite because the term "associated with" allegedly renders the relationship between the polypeptide-binding component and the marker component unclear. This rejection is rendered moot by cancellation of Claim 16 herein. Further, amended Claim 1, which incorporates the limitations of Claim 16, clarifies the relationship between the polypeptide-binding component and the marker component as discussed above.

6) Claim 17 is rejected as being indefinite because it allegedly is unclear how the marker components are "related." Claim 17 is amended herein to clarify that the "related" marker components are mutants or variants derived from the same gene. Basis for this amendment may be found in the specification, for example, at page 41, lines 3-20; page 42, lines 8-11; and page 43, lines 21-24.

7) Claim 24 is rejected as being indefinite because the term "signature polypeptide" allegedly is unclear. As the specification defines (*see, e.g.*, page 14, lines 27-28), a signature polypeptide is a type of marker. Nonetheless, this rejection is rendered moot by cancellation of Claim 24.

REJECTIONS UNDER 35 U.S.C. §102(b)

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention

is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

REJECTION OF CLAIMS 1-5, 10-12, 18-20 AND 28 UNDER 35 U.S.C. §102(b)

1) The rejection of Claims 1-5, 10-12, 18 and 20 under 35 U.S.C. §102(b) as being anticipated by Li (WO 97/44491) in light of Ward et al. (U.S. Patent No. 5,741,668).

Claims 1-5, 10-12, 18 and 20 are rejected under 35 U.S.C. §102(b) as being anticipated by Li (WO 97/44491) in light of Ward *et al.* (U.S. Patent No. 5,741,668). It is alleged that Li discloses detection of polypeptides using bacteriophage (genetic package) containing ligands (polypeptide-binding component) that specifically bind to the polypeptides. It is further alleged that Li discloses a label such as green fluorescent protein, which is known in the art (Ward *et al.*) to be a polypeptide and is therefore a marker component as recited in the claims. Li allegedly also discloses that the bacteriophage can be M13, amplification of the phage, immobilization of the polypeptide to a solid substrate, that the sample can be a blood sample, and a wash step to remove unbound material. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

The Claims

Claim 1 is directed to a multiplexed method of detecting a plurality of target polypeptides in a sample by (a) contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component; (b) identifying complexes of the plurality of target polypeptides with the displayed polypeptide-binding components on the genetic packages; (c) optionally amplifying either the genetic packages that have formed complexes or the marker components that are in the genetic packages that have formed complexes; and (d) detecting marker components in the genetic packages that have formed complexes, thereby detecting the plurality of target polypeptides. Dependent claims 2-5 specify the types of target polypeptides, binding of the target polypeptides or the genetic package to a solid support, the type of solid support, and a washing step after complex formation on a solid support. Dependent claim 10 specifies the types of samples, and dependent claims 11 and 12 further specify the nature of the genetic package. Claim 18 specifies the type of polypeptide-binding component, and claim 20 specifies techniques by which the marker is detected. Added claims 41 and 42 specify amplification of the genetic packages prior to detection of the markers, including the types of amplification reactions (claim 42). Added claim 43 depends on claim 17, which is not within the purview of this rejection.

Analysis

Differences between the disclosures of Li, Ward *et al.*, and the rejected claims

Neither Li nor Ward *et al.* discloses all elements of the rejected claims. Li is directed to the value of viral expression systems in detecting and monitoring receptor-ligand interactions of a target polypeptide (receptor) of interest. Li notes that viruses are sensitive detectors and can provide a detailed analysis of receptor-ligand interactions because they can express multiple copies of a ligand that binds to the target polypeptide of interest (page 13). Li describes a method of detecting and monitoring expression of a pre-selected polypeptide in a sample, using bacteriophage that are modified to display multiple copies of a ligand that binds to the pre-selected polypeptide of interest. Li discloses that in some embodiments, the phage are further modified to express a visually detectable protein, such as green fluorescent

protein (GFP). Thus, after the bound phage are identified, they can be detected by measuring GFP expression.

Li does not disclose a multiplexed method of detecting a plurality of target polypeptides in a sample by forming complexes between the target polypeptides and displayed polypeptide-binding components on genetic packages, where each genetic package has a predetermined marker component that indicates its displayed polypeptide-binding component and detection of marker components of the genetic packages that have formed complexes leads to identification of the plurality of target polypeptides. Li only discloses characterizing a particular target polypeptide (receptor) of interest by (1) binding to a phage that expresses multiple copies of a cognate ligand; and (2) detecting the bound phage by measuring expression of a suitable marker, such as GFP. There is no disclosure of simultaneously detecting a plurality of target polypeptides by binding to their cognate polypeptide-binding components on genetic packages and then simultaneously detecting marker components indicative of each polypeptide-binding component. The instant method is a multiplexed method which, as discussed above in addressing the rejection on grounds of indefiniteness, is clearly (from its plain meaning and in light of the specification) an assay that detects *different* types of target polypeptides in a sample by binding to their *different* cognate polypeptide-binding domains. Li on the other hand discloses multiple copies of the same ligand on a bacteriophage, not different types of ligands. Li discloses modification of a phage with a *single* ligand (albeit multiple copies of it) and a *single* marker to detect a *single* target (receptor) polypeptide, not simultaneous use of multiple polypeptide-binding components and their indicative markers to simultaneously detect a plurality of target polypeptides. Thus, Li does not disclose steps (a), (b) and (d) of Claim 1.

Ward *et al.*, which the Examiner appears to cite as evidence that GFP is a polypeptide, also does not disclose the subject matter of the rejected claims. Ward *et al.* is directed to a modified green fluorescent protein and does not disclose any methods of detecting target polypeptides in a sample.

Therefore, since anticipation requires the disclosure in a single reference of every element of the claims, Li, which does not disclose multiplexed detection of a plurality of target polypeptides by binding to their cognate polypeptide-binding components on genetic packages and then simultaneously detecting marker components indicative of each polypeptide-binding component (steps (a), (b) and (d) of Claim 1), and Ward *et al.*, which

does not disclose any method of detecting target polypeptides in a sample, do not anticipate Claim 1, nor Claims 2-5, 10-12, 18, 20, 41 and 42, dependent thereon.

2) The rejection of Claims 1-4, 18-20 and 28 under 35 U.S.C. §102(b) as being anticipated by Sano *et al.* (U.S. Patent No. 5,665,539).

Claims 1-4, 18-20 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by Sano *et al.* (U.S. Patent No. 5,665,539). It is alleged that Sano *et al.* discloses a complex (genetic package) containing nucleic acid markers (marker component) conjugated to antibodies (polypeptide binding component), which can be used to detect antigens such as proteins (encompassed by Applicant's definition of the target polypeptides). It is further alleged that Sano *et al.* discloses amplifying the marker by PCR, analyte bound to a solid support, and the simultaneous detection of many different antigens by using many different DNA markers attached to different antibodies.

Reconsideration of this rejection is respectfully requested in view of the amendments herein and the following remarks.

The Claims

Claims 1-4, 18, 20, 28 and added claims 41-43 are described above. It is noted that claim 43, which depends on claim 17, is outside the purview of this rejection. Claim 19 is directed to the method of claim 18 and specifies that the polypeptide-binding component that is an antibody or antibody fragment as set forth in claim 18 contains one or more antigen recognition regions. Claim 28, which specifies the types of amplification reactions used to amplify marker component, depends on the method of claim 27, which in turn depends on claim 1 and further specifies that the predetermined marker component contains a nucleic acid fragment.

Analysis

Differences between the disclosure of Sano *et al.*, and the rejected claims

Sano *et al.* is directed to the detection of antigens by complexation of the antigens with antibody-DNA conjugates. Each antibody is tagged to a different DNA conjugate. The antigen-antibody complexes are analyzed by amplifying and sequencing the conjugate DNA, thereby detecting the antigen of interest. Sano *et al.* discloses that the method may be used to simultaneously detect a plurality of antigens by conjugating each of their cognate antibodies with a different DNA (*i.e.*, each unique DNA sequence is indicative of a different antibody), thus identifying the different antigens by the differences in the sequences of the conjugate

DNAs attached to their respective antibodies. Sano *et al.* does not disclose any method in which a genetic package is used in a multiplexed method to detect a plurality of target polypeptides. As the specification clearly defines and describes (*see, e.g.*, page 11, lines 12-16 and page 29, lines 12-13), a genetic package refers to a biological composition or replicable vector, such as a phage, virus or bacterium, that encapsulates genetic material and can display or exhibit a polypeptide-binding component, such as a polypeptide, on its surface. Contrary to the Examiner's assertion, the antibodies disclosed in Sano *et al.* are not genetic packages.

Therefore, since anticipation requires the disclosure in a single reference of every element of the claims, Sano *et al.*, which does not disclose any genetic packages and therefore does not disclose a method of multiplexed detection of a plurality of target polypeptides by binding to their cognate polypeptide-binding components on genetic packages (step (a) of Claim 1), does not anticipate Claim 1, nor Claims 2-5, 10-12, 18-20, 41 and 42, dependent thereon.

REJECTION OF CLAIMS 6-9, 13-17, 22, 23 AND 27 UNDER 35 U.S.C. §103(a)

1) Claims 6-9 and 13 are rejected under 35 U.S.C. §103(a) as being obvious over Li. It is alleged that Li teaches bacteriophages that express on their surface at least 10, 100, 400, 800 or 1000 copies of a ligand that binds to the polypeptide to be detected. It is further alleged that although Li does not teach the number of polypeptides detected, its teaching of the number of ligands used to bind the polypeptides, when combined with "routine experimentation" to determine the optimal number of ligands to detect the polypeptides, leads to the claimed subject matter in which the number of ligands allegedly are optimized to correspond with the number of polypeptides. The Examiner cites Application of Aller (C.C.P.A. 1955) and Application of Boesch (C.C.P.A. 1980) for the proposition that when the general conditions of a process are known, it is not inventive to discover optimum working ranges of the process.

The Examiner also alleges, without providing reasons in support thereof, that it would have been obvious to one of ordinary skill in the art that the bacteriophages of Li would have a plurality of polypeptide-binding components.

2) Claims 13-17 are rejected under 35 U.S.C. §103(a) as being obvious over Sano *et al.* It is alleged that because Sano *et al.* teaches different antibody-DNA conjugates for different antigens, therefore it would have been obvious to one of ordinary skill in the art that

Sano *et al.* teaches a plurality of bio-displayed antibodies. It is further alleged that it would have been obvious to one of ordinary skill in the art to determine the optimal amount of different polypeptide-binding components because "the discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch (C.C.P.A. 1955).

3) Claims 22, 23 and 27 are rejected under 35 U.S.C. §103(a) as being obvious over Li in view of Buechler *et al.* It is alleged that it would have been obvious to one of ordinary skill in the art to combine Buechler *et al.*, which allegedly teaches using receptors in excess over the concentration of ligand to be determined in an assay, with Li, which allegedly teaches that assays such as sandwich assays can be used to determine binding between a protein, such as a ligand, and a receptor, to arrive at the claimed subject matter.

Reconsideration of this rejection is respectfully requested in view of the amendments herein and the following remarks. It is respectfully submitted that this rejection is rendered moot with respect to Claims 13 and 16, which are cancelled herein.

Relevant Law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritsch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

1) The rejection of Claims 6-9 and 13 under 35 U.S.C. §103(a) as being obvious over Li.

The Claims

Claims 6-9, which depend on Claim 1, described above, specify numbers of polypeptides that are concurrently detected by the multiplexed method of Claim 1. Claim1 as amended herein incorporates the limitations of rejected Claim 13 (cancelled herein) by specifying that the sample is contacted with genetic packages, each of which displays a polypeptide-binding component.

The combination of the teachings of Li with "routine optimization" methods does not result in the instantly claimed subject matter

Claims 6-9 depend on Claim 1 which, as discussed above, is directed to a multiplexed method of detecting a plurality of target polypeptides in a sample by (a) contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component; (b) identifying complexes of the plurality of target polypeptides with the displayed polypeptide-binding components on the genetic packages; (c) optionally amplifying either the genetic packages that have formed complexes or the marker components that are in the genetic packages that have formed complexes; and (d) detecting marker components in the genetic packages that have formed

complexes, thereby detecting the plurality of target polypeptides. Thus, Claim 1, which incorporates the limitations of Claim 13, and Claims 6-9, dependent thereon, are directed to a method of simultaneously detecting a plurality of target polypeptides in a sample, with Claims 6-9 specifying numbers of the plurality of target polypeptides that are detected by the method.

Li, on the other hand, teaches analysis of receptor-ligand interactions of a target polypeptide (receptor) of interest by forming receptor-ligand complexes between the receptor of interest and multiple copies of a ligand that is displayed on a phage or virus. Li does not teach or suggest any method of multiplexed detection of a plurality of target polypeptides. The Examiner alleges that given that Li teaches a bacteriophage that teaches display of a number of ligands on its surface, it is a matter of "routine optimization" to determine how many corresponding polypeptides are detected. To the contrary, Li teaches characterization of the receptor-ligand complexes of a particular target receptor of interest, using phage that display multiple copies of the particular cognate ligand of the target receptor of interest. Li teaches multiple copies of *one* ligand that binds to *one* receptor, not ligands that bind to multiple receptors that are then detected simultaneously. As discussed above, the instant method is a multiplexed method, which is clearly (from its plain meaning and in light of the specification) an assay that detects *different* types of target polypeptides in a sample by binding to their *different* cognate polypeptide-binding domains. Because Li does not teach any process in which a plurality of target polypeptides are detected simultaneously in a multiplexed method, Li cannot teach the determination of the numbers of target polypeptides (Claims 6-9) that are detected by a multiplexed method.

Further, Claims 6-9 cannot simply be arrived at by "routine optimization" of a "known" process, because the instant process of multiplexed detection was not previously known; as discussed, Li does not teach or suggest the instant process of multiplexed detection of a plurality of target polypeptides. Therefore, one cannot "routinely optimize" a process that, prior to the instant application, was unknown.

The instant methods *simultaneously* detect a *plurality* of target polypeptides by complexation with polypeptide-binding components on genetic packages, where each polypeptide-binding component is associated with a unique predetermined marker component and the marker components are detected simultaneously. There is no teaching or suggestion in Li of a method of simultaneous detection of a plurality of target polypeptides by

simultaneous detection of a plurality of distinct markers. Li only teaches detection of *one* particular receptor by binding to a phage that expresses multiple copies of *one* cognate ligand, where the phage can have *one* detectable label or marker to measure receptor-ligand complex formation. Contrary to the Examiner's assertion, it is not merely "routine optimization" of a "known process" allegedly taught by Li to arrive at the numbers of target polypeptides that are detected by the instant methods because, as discussed above, Li does not teach any multiplexed detection of a plurality of target polypeptides, Li only teaches detection of a particular target polypeptide (receptor) of interest. Therefore, the combination of Li with "routine optimization" of its method does not result in the instantly claimed subject matter.

Further, contrary to the Examiner's assertion, it would not have been obvious to one of ordinary skill in the art that the bacteriophages of Li would have a plurality of polypeptide-binding components. Li teaches bacteriophages that display multiple copies of a single ligand that binds to a particular receptor (target polypeptide) of interest. Li does not teach or suggest bacteriophages that display a plurality of ligands (polypeptide-binding components) on their surface, nor unique markers indicative of each polypeptide-binding component. Therefore, the combination of Li, which does not teach any multiplexed detection of a plurality of target polypeptides nor binding to a plurality of polypeptide-binding components on genetic packages, with routine optimization, does not result in the instantly claimed subject matter. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

2) The rejection of Claims 13-17 under 35 U.S.C. §103(a) as being obvious over Sano *et al.*

The Claims

Claims 13 and 16 are cancelled herein and their limitations are incorporated in Claim 1, described above. Claim 1 as amended clarifies that the plurality of target polypeptides in the sample are contacted with genetic packages, each of which displays a polypeptide-binding component, each polypeptide-binding component being indicated by a unique marker and detection of the markers whereby the plurality of target polypeptides are detected. Claims 14 and 15 depend on Claim 1 and specify the numbers of polypeptide-binding components in the method. Claim 17 is directed to the method of claim 1 where the marker components are variants or mutants derived from the same gene.

The combination of the teachings of Sano *et al.* with "routine optimization" methods does not result in the instantly claimed subject matter

Claims 14, 15 and 17 depend on Claim 1 which, as discussed above, is directed to a multiplexed method of detecting a plurality of target polypeptides in a sample by contacting the sample with genetic packages such that complexes are formed by specific binding of the plurality of target polypeptides to polypeptide-binding components that are displayed on the genetic packages; and the genetic packages each contain a predetermined marker component that is indicative of its displayed polypeptide-binding component. The marker components that are each indicative of a polypeptide-binding component are simultaneously detected in the genetic packages that have formed complexes, to thereby detect the plurality of target polypeptides in the sample.

As discussed above when addressing the rejection under 35 U.S.C. §102(b), the specification clearly defines and describes a genetic package as an entity, such as a phage, bacterium or virus, that encapsulates genetic material, including a marker component, and displays polypeptide-binding components, such as a polypeptide, on its surface. The antibodies used in the method of Sano *et al.* are not genetic packages.

The Examiner alleges that given that Sano *et al.* teaches different antibody complexes for different antigens, therefore Sano *et al.* teaches a plurality of displayed polypeptide-binding components and it is a matter of "routine optimization" of a "known process" to determine how many polypeptide-binding components are displayed. To the contrary, the numbers of polypeptide-binding components cannot simply be arrived at by "routine optimization" of a "known" process, *i.e.*, the method of Sano *et al.*, because Sano *et al.* does not teach the instant process of multiplexed detection of a plurality of target polypeptides by binding to polypeptide-binding components *displayed on genetic packages*. There is no teaching or suggestion at all in Sano *et al.* of using genetic packages to display polypeptide-binding components, much less using genetic packages to detect a plurality of target polypeptides.

Contrary to the Examiner's assertion, it is not merely "routine optimization" of a "known process" allegedly taught by Sano *et al.* to arrive at the numbers of polypeptide-binding components as specified in Claims 14 and 15 because, as discussed above, Sano *et al.* does not teach any process of multiplexed detection using genetic packages; there is no "known process" in Sano *et al.* of detecting a plurality of target polypeptides by binding to genetic packages. One cannot "routinely optimize" a known process where there is no

known process. Therefore, the combination of Sano *et al.* with "routine optimization" of its method does not result in the instantly claimed subject matter and the Examiner has failed to establish a *prima facie* case of obviousness.

Further, with respect to Claim 17, Sano *et al.* provides no teaching or suggestion whatsoever of using marker components that are related to one another as variants or mutants of the same gene. Sano *et al.* teaches antibody-DNA conjugates, where each DNA can have a unique sequence. Sano *et al.* does not provide any teaching or suggestion as to the relatedness of the sequences. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

3) The rejection of Claims 22, 23 and 27 under 35 U.S.C. §103(a) as being obvious over Li in view of Buechler *et al.*

The Claims

Claim 22 is directed to the method of claim 1, described above, that includes a further step of determining an amount of the marker component. Claim 23 specifies a further step in the method of claim 22 of correlating the amount of the marker component to an amount of at least one or more polypeptides in the sample. Claim 27 is directed to the method of claim 1 where the predetermined marker component contains a nucleic acid fragment.

The combination of the teachings of Li with Buechler *et al.* does not result in the instantly claimed subject matter

As discussed above, Li does not teach or suggest any method of multiplexed detection of a plurality of target polypeptides using markers that are indicative of each polypeptide-binding component that is displayed on a genetic package and binds to a target polypeptide. Li teaches multiple copies of *one* ligand that binds to *one* receptor, not ligands that bind to multiple receptors that are then detected simultaneously using distinct markers that indicate the polypeptide-binding components (ligands) with which the target polypeptides (receptors) form complexes. Buechler *et al.*, directed to a method of performing quantitative and semi-quantitative receptor-ligand binding assays, does not cure this deficiency. In fact, Buechler *et al.* does not teach or suggest binding to polypeptide-binding components that are displayed on genetic packages at all. Neither of the references, singly or in combination, teaches or suggests the multiplexed method of independent claim 1, from which the rejected claims depend. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Further, with respect to claims 22 and 23, neither of the references, singly or in combination, teaches or suggests quantitation of the marker component and correlation of the

marker component with the amount of target polypeptide. Li does not provide any teaching or suggestion regarding quantitation of a target polypeptide of interest and Buechler *et al.* teaches optimization of the amount of ligand relative to receptor in a competitive ligand-receptor binding assay, not quantitation of an associated marker to detect the amount of a corresponding target polypeptide. Therefore, the cited references, singly or in combination, does not result in the instantly claimed subject matter and the Examiner has failed to establish a *prima facie* case of obviousness.

COMMENTS REGARDING REFERENCES CONSIDERED "PERTINENT" TO APPLICANT'S DISCLOSURE

At page 11 of the Office Action, the Examiner states that the following references made of record are considered "pertinent" to Applicant's disclosure. Each of these references are addressed in turn below.

(1) The Examiner alleges that Teodorescu *et al.* (U.S. Patent No. 4,797,363) discloses bacteriophages employed as agents for the recognition and identification of molecules and cellular materials. Applicant notes that Teodorescu *et al.* is directed to a method of modification of a bacteriophage so that it binds to a target molecule or cell *via* its head or tail and the bound phage can be detected using a suitable marker. There is no disclosure or teaching of a multiplexed method of simultaneously detecting a plurality of target polypeptides in a sample by detecting markers that uniquely identify each polypeptide-binding domain, displayed on a genetic package, to which the target polypeptides are bound.

(2) The Examiner alleges that Ladner *et al.* (U.S. Patent No. 5,837,500) discloses a genetic package containing a binding domain on its surface. Ladner *et al.* discloses a method of selecting proteins with optimal binding affinity for a desired target by preparing libraries (in phage or bacteria) of variants of a ligand for the desired target, then selecting the variant with optimal binding affinity. There is no disclosure or teaching of detecting target polypeptides in a sample using genetic packages that display polypeptide-binding components.

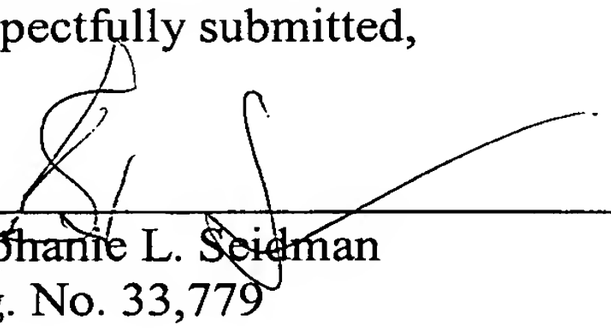
(3) The Examiner alleges that Nock *et al.* (U.S. Patent No. 6,686,154) discloses bacteriophages having polypeptides on their surface, and amplifying the phage. Nock *et al.* is directed to a method of screening phage or other replicable genetic packages in cell cultures to obtain those that specifically bind to a known target molecule of interest. The method, which screens the *phage*, is amenable to high-throughput format because the cell cultures do not have to be cleared of debris prior to performing the assay. Nock *et al.* does not disclose

or teach using genetic packages to screen samples and detect a plurality of target polypeptides.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,



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